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Novel L-Phe-Gly Mimetics

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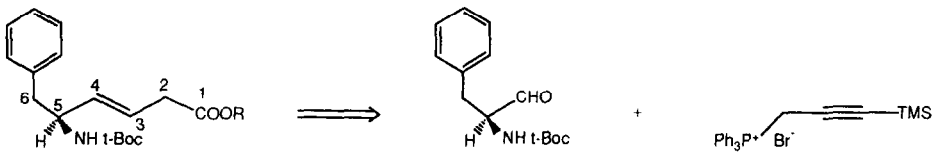
Abstract: The syntheses of some novel dipeptidomimetics of potential biological interest are described. The reactions started from the vinyl isostere of Phe-Gly and were performed in high yields. Stereochemically pure products were isolated.

Peptide-derived drugs have a number of serious shortcomings which are frequently associated with the metabolic instability and the hydrophilic character of the peptide bond. Isosteric analogues, peptidomimetics, which lack the amide functionality may offer many advantages.[1-4] In the present paper we describe the synthesis of peptidomimetics in which the Phe-Gly amide bond has been replaced by various functional groups which resemble the amide geometrically and/or electronically.

Compound (*S*)-**1a**, the *t*-butyloxycarbonyl (Boc) protected vinyl isostere of L-Phe-Gly, was synthesized from the aldehyde of Boc-L-Phe in analogy with a previously reported procedure for the corresponding isostere of L-Tyr-Gly.[5-8] The required Wittig reagent **2** was obtained by use of a modification of the literature procedure.[5,9] The methyl ester **1b** was prepared in 90% yield by treatment of **1a** with diazomethane. The stereochemical purity of **1b** (> 99%ee) was determined indirectly by ^{19}F-NMR spectroscopy after hydrolysis of the Boc-group and conversion of the resulting amine to an amide by reaction with (*S*)-Mosher acid chloride.[10]



1a R = H
1b R = Me

2

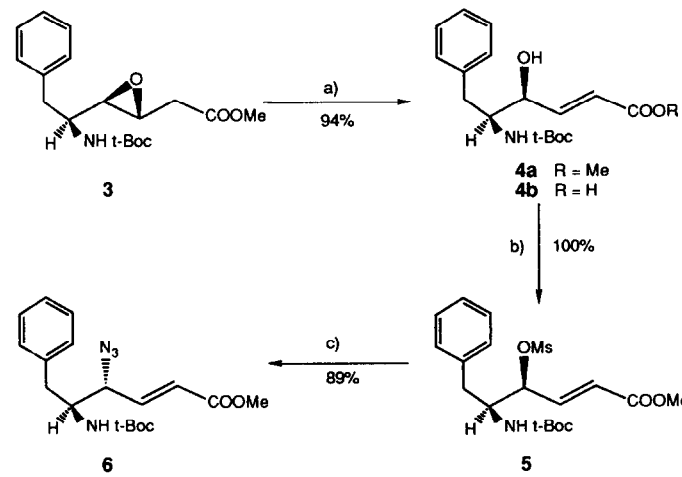
The epoxide **3** (Scheme 1) was obtained in 70% yield by treatment of **1b** with *m*-chloroperbenzoic acid in dichloromethane. The reaction appeared to be stereoselective since only one isomer was observed and isolated.

The epoxide ring of **3** was opened by use of fluoride ion in THF to afford the unsaturated alcohol **4a** in 94 % yield. Also this reaction appeared to be highly stereoselective since only one stereoisomer could be detected.

Conversion of the alcohol functionality to the mesylate **5**, allows for incorporation of a variety of nucleophiles in position C-4 by substitution reactions. The mesylate **5** showed considerable stability in that it

could be purified by silica gel column chromatography and it could be stored for long periods of time without decomposition. It was also quite stable to prolonged heating since more than 50% could be recovered after heating at 60°C over night. The usefulness of **5** as a synthetic intermediate was demonstrated by its conversion into the azide **6** (NaN_3, THF; 89% yield).[11]

Scheme 1

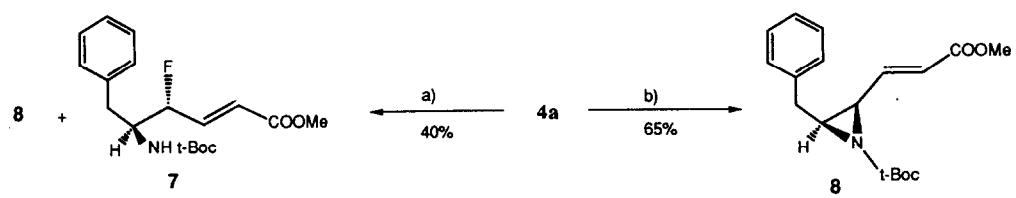


3 **5** **6**

Reagents: a) Bu_4NF, THF, r.t., 2 h, b) Mes-Cl, Et_3N, CH_2Cl_2, 0°C, 2 h, c) NaN_3, THF/H_2O, r.t., 12 h.

Two products were formed when the alcohol **4a** was treated with DAST (diethylamino sulfur trifluoride)[12] at room temperature during twelve hours; in addition to the expected fluoro-compound **7**[11,13] also the aziridine **8** was isolated. When the reaction was carried out at -78°C the aziridine was formed in 65% yield without concomitant formation of **7** (Scheme 2). Bird *et al.* have also observed temperature-dependent chemoselectivity when using DAST.[14]

Scheme 2



7 **8**

Reagents: a) DAST, CH_2Cl_2, r.t. b) DAST, CH_2Cl_2, -78°C.

All reactions discussed herein proceed with a remarkable stereocontrol. We found the selective formation of epoxide **3** particularly intriguing. The stereoselectivity in epoxidation reactions is strongly influenced by steric effects and coordination from hydrogen bond donating groups positioned α to the alkene. Directing effects due to coordination often outweigh steric effects.[15] An attack of the peracid at the α face of the double bond (Figure 1) would be expected if steric factors determined the stereochemical outcome of the epoxidation reaction. In contrast, attack at the β-face (Figure 1) would be expected if

directive effects through hydrogen bonding were dominating. According to our data only isomer **3** is formed in this reaction thus indicating that the attack of the peracid is directed by coordination to the carbamate and ester moieties (attack at the β-face, Figure 1).[16]

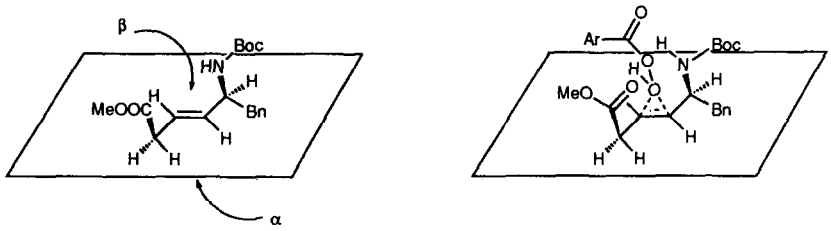
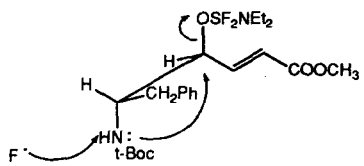


Figure 1: Stereoselectivity in the epoxidation reaction. At the left are shown the potential directions of attack of the peracid on alkene **1b**. Attack on the α-face would be facilitated if steric factors were dominating. However, an attack on the β-face results in a stabilized transition state with the peracid coordinated by hydrogen bonding (right).

The configurational assignment of **3** was made indirectly by comparison with the stereochemistry of the alcohol **4a** formed by treatment of **3** with fluoride ion (Scheme 1) since the C-4 configuration was presumed to be preserved during the ring opening reaction: A comparison of the melting point and the optical rotation of **4a** with that of an isomer of known stereochemistry indicated that we had obtained the (4*S*,5*S*)-isomer.[17,18] However, an unambiguous assignment was possible after ester hydrolysis of **4a** to yield the corresponding acid **4b** (mp 146-147°C; $[\alpha]_D$ = -101° ; *c* 0.64, MeOH). Comparison of the optical rotation and the melting point with published data of both isomers of **4b**[7c] confirmed the (4*S*,5*S*) configuration [(4*S*,5*S*)-**4b**: mp 149-151°C, $[\alpha]_D$ = -100° ; *c* 0.64, MeOH. (4*R*,5*S*)-**4b**: mp 167-168°C, $[\alpha]_D$ = +5° ; *c* 1, MeOH].

The configuration of the aziridine **8** was determined by ^{1}H-NMR spectroscopy. Measurements of the coupling constants between the ring protons (J = 6.2 Hz) indicates a *cis*-relation since *trans*-related protons would give a smaller coupling constant (2-3 Hz). The fact that the aziridine **8** has a *cis*-configuration has mechanistical implications. The formation of the aziridine from **4a** and DAST (Scheme 2) should occur through a concerted substitution reaction with complete inversion of the configuration at C-4 (left) or via a carbocation intermediate.[15] However, such a carbocation could not be of high stability. Additional evidence against a cation intermediate in the aziridine forming reaction was provided by experiments in which the mesylate **5** did not form any aziridine even after prolonged heating.



The compounds synthesized in this study could be useful as building blocks to be introduced in larger peptides, such as Substance P. This may provide new analogues of pharmacological interest and such novel peptidomimetics may facilitate studies of fundamental physiological processes. The new dipeptidomimetics introduced here are also of interest for further synthetic manipulations and azide **6** may be useful as a substrate in flash photolysis studies.

Acknowledgment: Financial support was obtained from the Swedish Board for Technical Development.

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16. As noted by the reviewer, steric hindrance may explain the stereoselectivity if a planar conformation is attacked.
17. Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 4370 (Litt. data for **4a**: mp 118-119°C, $[\alpha]_D$ = -65.3°; *c* 1.56, $CHCl_3$. Found: mp 111-112°C , $[\alpha]_D$ = -54.8°; *c* 1.0, $CHCl_3$).
18. The difference between reported[16] and observed physical data did not change after repeated recrystallization of **4a**.

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